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Vondeling, Gerard T; Cao, Qi; Postma, Maarten J; Rozenbaum, Mark H

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SYSTEMATIC REVIEW

The Impact of Patent Expiry on Drug Prices: A Systematic Literature Review

Gerard T. Vondeling[1] · Qi Cao[1] · Maarten J. Postma[1] · Mark H. Rozenbaum[1]

Abstract

Objective The aim of this study was to evaluate the impact of patent expiry on drug prices by means of a systematic literature review.

Methods A systematic literature search was performed in PubMed to identify all published literature on the impact of patent expiration on drug prices. Additional literature was identified using a less distinct syntax in Google Scholar and EconLit. Data extraction followed a standardized assessment form containing the domains study type, study aim, reported outcomes, number of drugs and drug classes assessed, and originators or generics assessed.

Results The 16 identified studies that assessed impact of patent expiry on drug prices showed that price developments after patent expiration varied between countries. The included studies assessed price developments for the USA, Canada, Australia, the UK, the Netherlands, Germany and France, Spain, Italy, Norway, Sweden and Denmark. The number of drugs included within different studies ranged between 1 and 219. The identified studies indicated that drug prices decreased significantly after patent expiry with drug price ratios ranging from 6.6 to 66% 1–5 years after patent expiry.

Conclusion Drug prices decrease significantly after patent expiry. The extent of this price reduction varied greatly between products and countries. For this reason, country-specific analyses on price developments after patent expiry should be used when these are considered in decision making. Future research should be dedicated to gathering more country-specific data to reduce the uncertainty with regard to price developments.

Key Points for Decision Makers

Drug prices decrease significantly after patent expiry.

Country-specific data on drug price developments is lacking for the European market.

Country-specific data on drug price developments should be used in decision making where drug prices play a prominent role.

1 Introduction

In high-income countries, total health expenditure represented 12.3% of the gross domestic product (GDP) in 2014 [1]. Following the great recession of 2008, health expenditures have once again become a major target of cost-containment efforts at national level [2]. In the Netherlands, the total healthcare expenditure rose from €67 billion in 2005 to €96 billion in 2016. The budget spend

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✉ Gerard T. Vondeling
gertvondeling@msn.com

Qi Cao
q.cao@rug.nl

Maarten J. Postma
m.j.postma@rug.nl

Mark H. Rozenbaum
mark.rozenbaum@pfizer.com

[1] University of Groningen, PO Box 72, 9700 AB Groningen, The Netherlands

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on pharmaceuticals during the same time period remained rather stable though, and accounted for approximately 10% of these healthcare expenditures [3]. Though newly introduced pharmaceuticals may pressure a given healthcare budget, patent expiration and associated price decreases may offset this burden. After a patent expiry or loss of other exclusivity rights, generic copies of the originator can be produced and marketed without a license from the originator company [4]. The market entry of generic copies of originator drugs after patent expiry and subsequent generic substitution play a role in the cost containment in health care and pharmaceuticals [5].

Patents can foster innovation as they provide the manufacturer the opportunity for a temporary monopoly and a period of market exclusivity [6]. During the period of market exclusivity pharmaceutical companies can recoup the opportunity costs made during the drug development process. The right of market exclusivity for new products stimulates new investments in Research and Development (R&D). Several factors may influence the duration of market exclusivity, including: the moment of patent filing, the duration of the R&D process afterwards, the registration process and time to approval/reimbursement by the US Food and Drug Administration (FDA)/European Medicine Agency (EMA) and national health technology assessment (HTA) agencies, and the duration before approval of generic drugs [7].

The aim of this study was to evaluate available quantitative data regarding impact of patent expiry on drug prices by means of a systematic literature review.

2 Methods

2.1 Literature Search

A systematic literature search was performed on peer-reviewed literature in the PubMed, EconLit and Google Scholar databases in February 2018. A comprehensive search syntax that included the terms “patent”, “brand”, “licensed”, “market exclusivity”, “drug”, “medicine”, “pharmaceutical”, “expiration”, “expiry”, “generic entry”, “generic substitution”, “lifecycle”, “originator”, “price”, “cost”, “cost effectiveness”, “ICER” was run through the PubMed Database (Appendix 1). A subsequent literature search was performed using a less distinct syntax with the terms “generic substitution” and “patent expiry” for titles and abstracts in the EconLit database and Google Scholar. Additionally, the references in the bibliography of the papers selected from the included databases were reviewed manually. Searches were limited to publications from the year 2000 onwards.

2.2 Literature Selection

The selected literature was limited to full publications of original research. Studies were included if they reported quantitative outcomes on the impact of patent expiration on drug prices. Exclusion criteria included: (a) papers were not written in English or Dutch, or (b) the endpoints (reported outcomes) on price developments did not include or were not comparable to moment of initial generic entry. Reported endpoints on price developments after patent expiry were extracted as outcome for this study. The selection of literature and data extraction was performed by two authors (GTV and QC). In case of disagreement, a third author was consulted(MHR).

2.3 Data Analysis

A standardized assessment form was developed to extract data, which included the following domains: study type, study aim, reported outcomes and results, number of drugs assessed, drug class, originators or generics assessed, and time point after patent expiry of reported price development outcomes. The moment of patent expiry was defined as the moment of initial generics entry. A generic drug was defined as a pharmaceutical drug that is equivalent to a brand-name product in route of administration, quality, performance, and intended use. Reported outcomes on price developments were translated into price ratios compared to the price of the original product at moment of patent expiry, where necessary.

3 Results

3.1 Results of Data Extraction

The systematic PubMed search yielded 262 unique citations. After screening for titles and abstracts 214 citations were excluded based on the exclusion criteria. The remaining 48 articles underwent full-text examination for eligibility, which resulted in the inclusion of ten articles [8–17]. The remaining 38 articles were excluded as they examined policy changes, prescription patterns, or total healthcare expenditures rather than price developments after patent expiry. The literature search in the EconLit database yielded 36 articles of which 11 were deemed eligible for full-text examination. Seven articles met the inclusion criteria of which two were duplicates from the PubMed search [18–24]. One additional study that met the selection criteria was identified in the literature search in

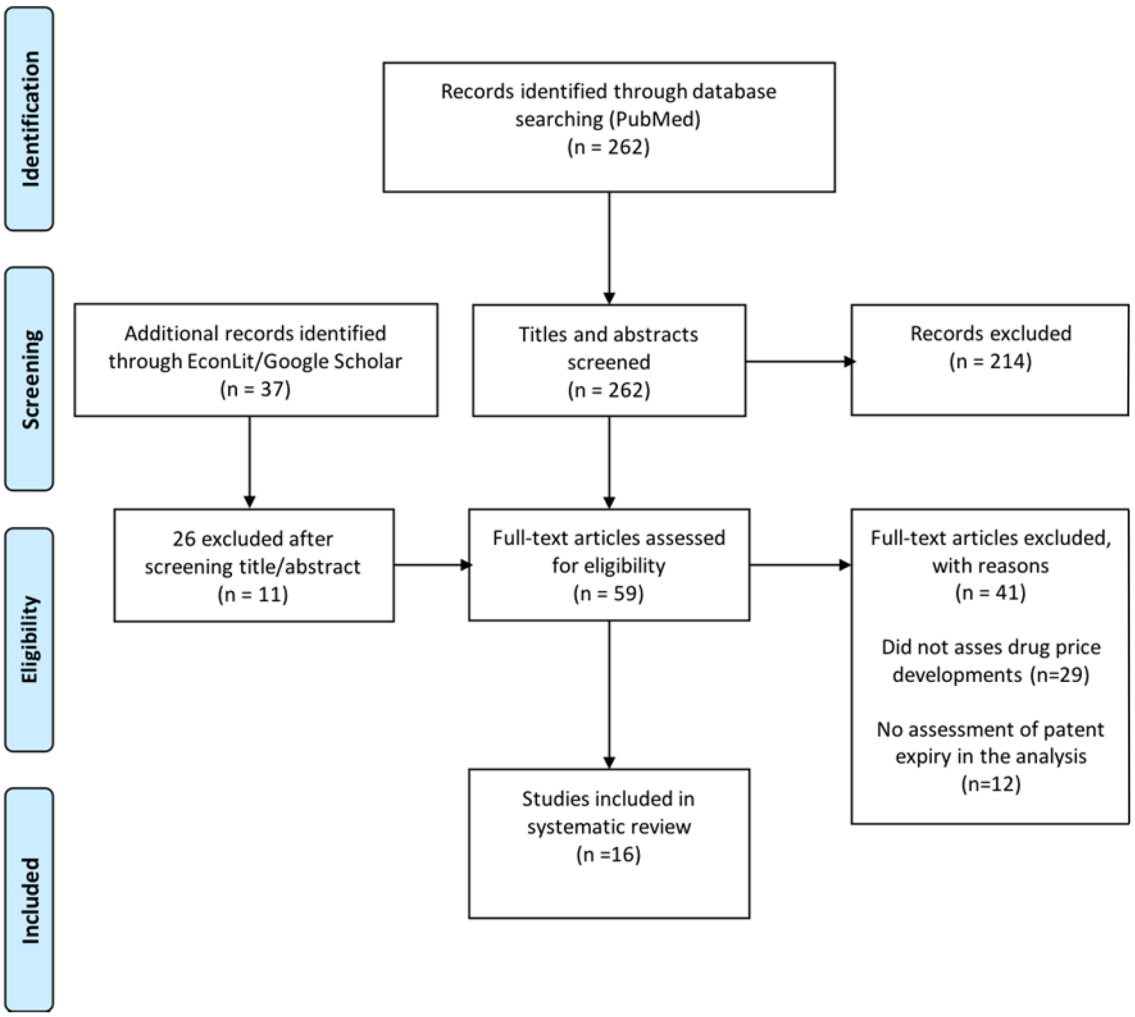

Fig. 1 Flow diagram of the study selection process

Google Scholar [6]. As a result, in total 16 studies were selected for data extraction (Fig. 1).

Table 1 summarizes the included studies in this review. Studies focused on 12 different countries over three continents. The majority of the studies focused on or included the USA ($n=9$) [6, 8, 10, 11, 15–18, 21, 22, 24]. Furthermore, one study focused on Canada [14], one study on the Netherlands [12], one on Spain [20], and four studies assessed the price developments in multiple countries [9, 13, 19, 23]. In total 16 studies examined the impact of patent expiration on drug list prices over time [6, 8–15, 18–24].

3.2 Time Period and Number of Drugs Included

Eleven studies identified and assessed all drugs facing initial generic entry within their study period, to provide a representative overview of the impact of patent expiry on price for the total market [6, 8, 10, 11, 13–15, 18, 20, 21, 24] (see also Tables 1 and 2). The remaining five articles focused on a specific therapeutic area or specific drugs [19, 22, 23].

All studies included in this review assessed price developments of between one and 129 different drugs. Price developments of the included drugs were assessed between 1984 and 2009, and the average study period length was 7.5 years [8].

3.3 Definition of Patent Expiry

As the moment of patent expiration varies between countries, and drugs are often protected by several different patents, it can be challenging to define a set point for patent expiry. Notably, studies included in this review that assessed the impact of expiry on drug prices used varying definitions for the set time of patent expiry. Seven studies used the time of initial generic entry as a surrogate endpoint for the moment of patent expiry [8, 10, 11, 14, 20, 22], whereas in six the date of patent expiry was available within the

Table 1 Overview of studies included in the review

Study, publication year and reference	Country	Included generic or originators	Number of drugs assessed	Therapeutic category	Study period
Kelton et al. (2014) [8]	USA	Generic	83	Various	1991–2008
Clarke et al. (2010) [9]	Australia and UK	Generic	1	Simvastatin	2002–2009
Berndt et al. (2007) [10]	USA	Generic	11	Various	1999–2003
Hong et al. (2005) [11]	USA	Originator	27	Various (oral and non-antibiotic)	1987–1992
Boersma et al. (2005) [12]	NL	Generic	3	H2 receptor antagonists	1996–1999
Magazzini et al. (2004) [13]	USA, UK, GER, FR	Originator	269[a]	Various	1987–1996
Lexchin et al. (2004) [14]	Canada	Originator	81 drugs in 144 presentations[b]	Various	1990–1998
Suh et al. (2000) [15]	USA	Generic and Originator	35	Various	1984–1987
Lakdawalla et al. (2006) [6]	USA	Generic and Originator	101	Various	1992–2002
Berndt et al. (2011) [18]	USA	Generic and Originator	219 brands	Various	1984–2009
Kanavos et al. (2008) [19]	UK, Canada, GER, FR, Spain, Italy, USA	Generic and Originator	12 molecules	Various	2000–2005
Puig-Junoy Jaume et al. (2012) [20]	Spain	Generic	8	Various	Jan–Jul 2008
Saha et al. (2006) [21]	USA	Generic and Originator	40	Various	1991–1998
Wiggins et al. (2004) [22]	USA	Generic and Originator	98	Anti-infectives	1984–1990
Vandoros et al. (2013) [23]	Germany, UK, NL, Sweden, Norway, Denmark	Originators	12	Plain ACE-inhibitors, atypical anti-psychotics, PPIs and antidepressants	1997–2002
Grabowski et al. (2007) [24]	USA	Generic and Originator	40	Various	1992–1998

ACE angiotensin converting enzyme, *PPI* proton pump inhibitor, *EP* Market Exclusivity Period, *USA* United States, *NL* Netherlands, *UK* United Kingdom, *GER* Germany, *FR* France

[a]The same active ingredient in different countries was counted separately (four countries total considered in the paper

[b]Different administration forms of the same drugs counted as separate products

used database (MIDAS-IMS International database and the IMS Generic Spectra database) [6, 13, 19, 21, 23, 24]. The remaining three studies that assessed the impact of expiry dates on drug prices did not specify how the patent expiry date was set [9, 12, 15].

3.4 Outcome Measurement and Data Use

Various outcome measures were used in the studies included in this review. Whereas seven studies assessed the impact of generic entry on both originator and generic prices [6, 15, 18, 19, 21, 22, 24], five studies only reported generic price developments [8–10, 12, 20], and four studies focused only on price developments of originator drugs after generic entry [11, 13, 14, 23].

Furthermore, 12 studies defined their outcome as a price ratio compared to the originator price at the moment before patent expiry (seven for both generic and originator drugs, three for generics only and three for originators only) [6, 8, 10, 13–15, 18, 20–24], one study reported the outcome as wholesale price per tablet [9], and two studies used price per Defined Daily Dose (DDD) as the comparative outcome measurement [12, 18]. In addition, two studies reported on the price rigidity of originator drugs and reported price changes in percentages at certain time points after patent expiry [11, 23].

The type of data used to estimate the impact of patent expiry on drug prices also varied between studies. Thirteen studies used drug-utilization data, which allowed for the correction of the proportionate use of different strengths and administration forms of both originators and generics [6, 8–10, 12, 13, 15, 18, 19, 21–24], whereas three other studies only used price data [11, 14, 20]. A further three studies used the assumed average maintenance dose per day for a

Table 2 An overview of the outcomes of price developments after patent expiration

Study	Region	Number of drugs	Price ratio after patent expiry	Time point of measurement of price ratio (after generic entry)
Suh [15]	USA	35	66% 1st year 32% 4th year	1 year 4 years
Boersma [12]	NL	3	Enalapril 39% Fluoxetine 49% Ranitidine 31%	24 months 24 months 52 months
Berndt [10]	USA	1 10	37% (5− generic entries) 25% (5 + generic entries) 27% average with product line extensions 29% on average without product line extensions No overall average	24 months
Lakdawalla [6]	USA	101	58% (generic) 100% (originator)	18 months
Lexchin [14]	USA, Canada	81	100% (originator)	Not specified (before and at moment of initial generic entry and subsequent entry)
Hong [11]	USA	27	100% (no change originator) (average)	5 years before and after entry
Magazzini [13][b]	USA, UK, GER, FR	269[a] (originators only)	US + 20% UK − 25% GER − 25% FR 0% change	9 years after initial generic entry
Clarke [9]	Australia UK	1	50% Australia (± 15% decrease in price per year) 4% UK (More than twice the rate, no exact number shown)	4 years
Kelton [8]	USA	83	Between 11 and 41% (No overall average) extra firm leads to 13% price-drop on average.	21 quarters after generic entry
Berndt [18]	USA	219	64.9% for all drugs across nine therapeutic areas	24 months after initial generic entry
Kanavos [19]	UK, Canada, GER, FR, Spain, Italy, USA	12	Varies greatly between products and countries; minimum generic price 47% lower in countries with reference pricing	Not specified
Puig-Junoy [20]	Spain	8	Amlodipine 53% Fluoxetine 21%	Not specified
Saha [21]	USA	83	Ranged widely between drugs; 68/83 where priced lower, 15 where less then 50% of the original price	1 year after initial generic entry
Wiggins [22]	USA	98	Depending on the number of sellers; 50% with 2/3 sellers, less then 33% with 4 + sellers, and 6.6% with > 40 sellers	Not specified, analysis based on number of sellers
Vandoros [23]	GER, UK, NL, SWE, Norway, Denmark	12	Overall originators 5% higher price in markets where a generic product is present: Denmark − 2.5% when generic is available Germany + 1.3% NL + 11.3% Norway + 3,8% Sweden − 0.8% UK + 4.1%	Time point not specified
Grabowski [24]	USA	40	On average for all included drugs: 55%	12 months after initial generic entry

USA United States, *NL* Netherlands, *UK* United Kingdom, *GER* Germany, *FR* France

[a]Considered the same active ingredient in different countries as different (four countries total)

[b]Outcomes are estimations from a graph

drug (DDDs) as a comparative measure [12, 13, 15], and three more used real-world prescription or utilization data for the investigated drugs to weight prices [6, 8, 22]. Lastly, the remaining two studies did not elaborate on how utilization data was used to weight prices [9, 10].

3.5 Outcomes

The 12 studies that assessed generic prices after patent expiry showed price ratios ranging from 6.6% up to 66% after 1–5 years after initial generic entry (see Table 2) [6, 8–10, 12, 15, 18–22, 24]. Both Berndt et al. [10] and Wiggins et al. [22] additionally detected an inverse relation between the number of generic entrants and the drug price, although beyond five generic entrants no further impact on the drug price was observed [10]. Similarly, Kelton et al. showed that for every additional generic introduced, the relative reimbursement price of a drug would decrease with 13% on average [8].

Of the six studies that assessed the impact of patent expiration on originator prices [6, 11, 13–15, 23], the four studies that focused on the USA concluded that originator prices were rigid and overall did not alter significantly after patent expiry [6, 11, 14, 15]. However, both the studies by Magazzini et al. and Vandoros et al. showed that the impact of patent expiration varied between different countries [13, 23]. For example, Magazzini found that in France the price after patent expiry was rigid for originators, while in Germany and the UK originator prices decreased by 25% on average in the 9 months after patent expiry, and in the USA originator prices increased by 10–20% over the same period [13]. Based on the analyses in Denmark, Germany, Norway, Sweden, the UK, and the Netherlands, Vandoros reported that overall originator prices were 5% higher in markets where generic counterparts were available. In Denmark and Sweden originator prices were 2.5 and 0.8% lower when generics were available, while in Germany, Norway, the UK and the Netherlands originator prices were found to be 1.3, 3.8, 4.1 and 11.3% higher, respectively, for products with generics available. Country differences were also analyzed by Clarke et al. who showed large differences in wholesale price developments as well as patterns in generic uptake of simvastatin between the UK and Australia [9]. In Australia the price of statins decreased by 15% annually after patent expiry, down to 50% of the originator price in the first 4 years after patent expiry. In the UK the original price was initially higher, but the price decreased at more than twice the rate to about 4% of the original price over the same period [9]. Additionally Kanavos et al. indicated that both originator and generic prices varied greatly between countries and products and that the minimum generic price is on average 47% lower in countries that use reference pricing for generics [19].

4 Discussion

This systematic review disclosed the evidence scarcity with regard to the impact of patent expiry on drug prices. All included studies suggest that generic entry causes significant price competition that leads to an overall decrease in pharmaceutical costs, though the extent to which drug prices decrease after patent expiry differed between studies and countries. Different trends were observed in price developments after patent expiry between originators and generics. Generic drug prices are negatively correlated with the number of generic manufacturers in the market, although originator prices may increase when more generic manufacturers appear to compensate for losses in market share.

Availability of drug utilization data is important to calculate the overall budget impact, as prices of different products can be weighted by their proportionate use. The majority of the studies (13 out of 16) included drug-utilization [6, 8–10, 12, 13, 15, 18, 19, 21–24]. By correcting overall prices for generic share, strengths, package sizes, and administration forms, the calculated weighted average price represents the price paid by society for a certain drug over time. Of the studies included into this review, five were able to provide an accurate estimate of the price development after patent expiration for the total market by correcting for most these factors [6, 12, 13, 15, 18]. Drug-utilization should preferably be measured in number of DDDs, as this is a global standardized measure that enables price-comparison between different strengths and administration forms.

In order to make useful predictions on future drug price developments or implement data on price developments into cost-effectiveness analyses, the data should be complete, up to date, and specified towards the specific market within the country of interest. Currently available literature shows limitations to do so, especially for European countries. Price developments over the lifetime of drugs may vary greatly between countries as they may apply different pricing and reimbursement policies that can influence drug prices over time [25]. A well-established methodological framework for evaluating drug prices over time that also allows for comparison between countries is lacking. Cross-country price comparisons are only meaningful if comparable data is used to compare the same drug. As such a standardized administration form would be required, as well as an identical format of price display (such as cost per universal outcome measures, e.g., price per defined daily dose). For these reasons the different studies are hardly comparable in terms of price developments over time.

Another limitation is the use of publicly available prices. These prices do not reflect the confidential

discounts that are often disclosed between manufacturers and governments or decision makers. Although these prices do not properly reflect on the total healthcare expenditure or possible savings made, these prices are the prices that insurers or consumers have to pay. Consequently, these publicly available list prices are the prices used within assessments of affordability and cost effectiveness studies.

Despite the limitations, data on drug price developments can be utilized in several ways. The horizon scan is a newly introduced method in the Netherlands to track all the innovative drugs that will come to the market as well as drugs that will have their patents expire in the near future [26]. Use of correct information on price developments after patent expiry can help to estimate the impact on the healthcare budget of both these new innovative drugs and those that will have their patent expired. Besides forecasts on healthcare expenditure price developments during the lifecycle of a drug can be used in health economic models to provide more realistic estimations on the cost-effectiveness of a new drug.

The majority of the included studies that focused on the impact of patent expiry on price used data from before 2000, while no study available included data from 2010 onwards. Furthermore, the USA is overly represented in the included studies with only three studies focusing on a single other country. Overall it can be concluded that studies focusing on the impact of patent expiry on the total pharmaceutical and healthcare costs in the European market are still lacking. None of the included studies investigated the impact of patent expiry on price in different therapeutic classes. Stratifying outcomes for therapeutic classes could be interesting as one (e.g., cardiovascular drugs) might be more appealing for generic competition then others. If different therapeutic classes show different trends, then stratification should be necessary in order to make more reliable estimations for price developments of future drugs. Next to therapeutic classes biologicals and orphan drugs should also be placed into a different segment as different regulations apply to these classes of drugs. Moreover, it is important that all drugs that faced generic entry over time are included to provide a weighted estimated price development that is representative for the entire drug market in the country and specific field of interest.

5 Conclusion

With limited evidence and knowledge on the impact of patent expiry on the total pharmaceutical and healthcare costs in the European market, a significant decrease in drug prices after patent expiry was found. The extent of this price reduction varied greatly between products and countries. For this reason, country-specific analyses on price developments after patent expiry should be used when these are considered in decision making. Future research should be dedicated to gathering more country-specific data to reduce the uncertainty on price developments.

Data Availability Statement Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with Ethical Standards

No funding was received for this study.

Author contributions GTV, MHR, and MJP developed the design of this study. GTV and QC carried out the data collection and conducted the data extraction and were supplemented by MHR for discussion in care of disagreement. All authors contributed in the conceptualization of the paper. GTV and MHR drafted the manuscript. All authors revised it critically for intellectual content. All authors read and approved the final manuscript.

Disclosure of potential conflicts of interest Mark Rozenbaum is employed by Pfizer. Gert Vondeling, Qi Coa, and Maarten Postma declare that they have no competing interests.

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